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TITLE: EFFECTS OF HIGH ALTITUDE HYPOXIA ON LUNG AND CHEST  
WALL FUNCTION DURING EXERCISE

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13. ABSTRACT (Maximum 200 words) We have more precisely than has been done before, defined the mechanical limits of the lung and chest wall for the ventilatory requirements of exercise in healthy persons. In most instances in the normal or moderately fit individual the ventilatory requirement is such that mechanical limitations are barely reached upon expiration, the inspiratory muscles achieve only 40-60% of their capacity for pressure generation and fatigue of the respiratory muscle is not a factor - at least during short term maximum exercise. The greater the maximal $\dot{V}O_2$ , the greater the ventilatory cost and the closer one comes to mechanical limitation of ventilation. Under these conditions, oxygen cost of breathing can approach 13-15% of the total $\dot{V}O_2$ and during long term exercise the diaphragm becomes fatigued. If hypoxia accompanies the exercise, the ventilatory requirement would increase substantially, diaphragm fatigue occurs earlier, mechanical limitations to expiratory flow and inspiratory pressure development occur at lower work-rates and the diaphragm becomes fatigued in a much shorter exercise time. These factors may contribute significantly to the limitation of exercise performance - especially endurance exercise.				
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5. INTRODUCTION - The overall aim of our research was to define the role of the lung and chest wall in the physiologic response to short and long-term exercise in normoxic and hypoxic environments in healthy young adult males. To this end we addressed the following questions:

- 1) What is the capacity of the lung and chest wall for pulmonary gas exchange, for the development of pressure by the inspiratory muscles and flow by the expiratory muscles, and of the diaphragm to sustain repetitive, high levels of pressure development?
- 2) What demands are made on the lung and chest wall during short and long term maximum work in terms of the adequacy of pulmonary gas exchange, inspiratory and expiratory flow and pressure development, and pressure development by the diaphragm and the oxygen cost of breathing?
- 3) Combining the aims 1 and 2 above we addressed the broader question "Does demand ever exceed capacity in the healthy, exercising pulmonary system?" We hypothesized that the fitness of the healthy person would dictate whether demand ever exceeded capacity ie the greater the work capacity the greater the max requirements on the pulmonary system and the greater the likelihood that demand would exceed capacity.

## 6. BODY

**METHOD - Innovation and Development.** We adapted many existing techniques and invented new ones for use to answer questions of pulmonary system demand vs capacity during exercise. The following methods were successfully developed for this purpose:

- 1) We defined in resting subjects the capability of the inspiratory muscles for pressure generation in terms of the effects of flow rate (velocity of shortening) and muscle length (lung volume).
- 2) We determined the transpulmonary pressure during expiration at which airways would close and airflow would become limited across the entire range of lung volumes.
- 3) We developed a rebreathing technique for use during heavy exercise to measure end-expiratory lung volume using two inert gases.
- 4) We developed the hardware and software to measure breath by breath, the flow and volume characteristics during all levels of exercise and then were able to ensemble the average breaths at all the work-rates to arrive at a flow:volume and transpulmonary pressure:volume average "loop".

- 5) Combining all of the above methods (1-4) we were able to quantify the capacity of individual subjects for development of flow and pressure and then plot (within the limits of this capacity), the actual flow, volume and pressure achieved by the subject, so that we could determine with substantial accuracy precisely how much of the reserve of the lung, airways and chest wall the subject had used during exercise. This has proved to be a powerful tool to apply to questions of demand vs capacity in the exercising human.
- 6) We developed the technique for quantifying the oxygen cost of exercise hyperpnea by training the subject to reproduce all the important mechanical characteristics of an average breath that they achieved during different levels of exercise and then measuring the change in whole body oxygen consumption required to maintain this breathing pattern, and pressure development in the steady state and used this as a quantitation of the oxygen cost of exercise hyperpnea.
- 7) We developed a definitive technique for assessing diaphragmatic fatigue in the human as a result of exercise. We modified the bilateral phrenic nerve stimulation technique, whereby supermaximal electrical stimulation of the phrenic nerves is applied transcutaneously using surface electrodes, the EMG of the diaphragm is recorded to ensure that nervous supermaximal electrical activation of the diaphragm is achieved and the tension developed by the

muscle is monitored by measuring the pressure development as the difference between the esophageal and gastric pressure measurements. Reproducibility within days and between days in single subjects was established prior to any application of these techniques to exercise. We have now applied these techniques to young adults of varying ages and more importantly across a wide range of fitness levels, from normal average max  $\dot{V}O_2$  to levels which were two x normal (ie in trained athletes) so that we could test the hypothesis of demand vs capacity in the healthy system.

#### Findings obtained in applying these techniques.

1. The capacity of the pulmonary system as defined through these techniques was tested in many individuals. We found this to be strikingly similar across a wide range of fitness levels and a wide range of ages. In fact, among the few females tested we also failed to find gender differences in the degree of expiratory flow limitation by the airways, or the capacity for pressure development by the inspiratory muscles. We determined that the oxygen cost of exercise hyperpnea increased in a curvilinear fashion with increasing ventilatory work as exercise intensity progressed. Thus at above 60 to 70% of maximum oxygen consumption the oxygen cost of breathing ( $\dot{V}O_{2RM}$ ) averaged only 4-6% of the total body  $\dot{V}O_2$  ( $\dot{V}O_{2TOT}$ ); whereas at max  $\dot{V}O_2$ ,  $\dot{V}O_{2RM}$ , averaged 9-11% of  $\dot{V}O_2$  max as the oxygen cost per liter ventilation (or per unit ventilatory work) doubled between the two work-rates. In those subjects who reached the highest ventilatory requirements and whose flow and

volume were partially limited on expiration in max work, the oxygen cost of ventilation was 13-15% of  $\dot{V}O_2$  max. This may represent a substantial "steal" of blood flow from locomotor muscles and may make the chest wall a limiting factor in exercise in those subjects who demand high levels of ventilation because of their high levels of metabolic requirement. The high levels of ventilation due to hypoxia may also cause excessive  $O_2$  costs of exercise hyperpnea.

2. In the young adult of average fitness, substantial reserve exists during maximal exercise for the development of expiratory flow and inspiratory muscle pressure development, as this subject's requirements for ventilation dictate that he barely reach the limits of his airways for producing flow and comes only within 40-60% of the inspiratory muscle's capacity for generating pressure. As one increases in fitness,  $\dot{V}O_2$  max and therefore maximum ventilatory requirements, more and more of the mechanical reserves of the lung and thorax are used in max exercise. Eventually, in the most highly trained humans we studied, they used their entire reserve for ventilation as expiratory flow limitation was substantial and the maximum capacity of the inspiratory muscles was reached at max exercise. We applied the techniques for measuring maximum diaphragmatic pressure to endurance exercise, whereby subjects exercised at 80% and then again at 90% of the  $\dot{V}O_2$  max to exhaustion, the former being reached in an average of 30 min and the latter



in 15 min. In all cases, at the heavier level of exercise, the diaphragm showed "fatigue", ie the pressure developed by the diaphragm for a given supermaximal level of phrenic nerve (motor nerve) stimulation was significantly reduced by 10-35%. This fatigue was less consistent following exhaustive exercise at the lighter work rate but did occur on the average in most subjects. The recovery of the diaphragm from fatigue following exercise took between 1 and 1 1/2 hours to recover its pressure development for a given supermaximal motor input. The degree of diaphragmatic fatigue incurred by the exercise bore a significant positive relationship - at either work rate - to the amount the diaphragm was actually used during the exercise. There were some indications that over the time-course of exercise the diaphragm actually reduced its contribution to the total pressure and ventilation produced - this may be due to the onset of fatigue at this time.

- 3) Pulmonary gas exchange fails only very, very rarely in the healthy human during exercise - even when the exercise is the cause of mechanical limitation to flow and pressure and diaphragmatic fatigue. Exercise induced hypoxemia will occur in the well trained healthy person when diffusion limitation occurs at the alveolar-capillary level in very heavy exercise.
- 4) Preliminary studies have been done on the effects of hypoxia on all of these responses. We found that the hyperventilation accompanying exercise in

hypoxia is such that mechanical limits to flow and inspiratory pressure may be reached even in the less well trained individual who does not reach extremely high maximum metabolic demands but does have high ventilatory requirements because of the hypoxemia. Diaphragm fatigue also occurred even when the exercise was reduced to one-half the endurance time of that attained under normoxic sea level conditions. In short, our preliminary data to date clearly show that hypoxemia pushes the pulmonary system towards limitation and to incur excessive cost even in the untrained healthy person.

7. CONCLUSIONS. We have, more precisely than ever before, defined the mechanical limitations to normal exercise in healthy persons. In most instances in the normal or moderately fit individual, the ventilatory requirement is such that mechanical limitations are barely reached on expiration; inspiratory muscles use < one-half of their pressure generation capability in heavy short term exercise and fatigue of respiratory muscles is not a factor. On the other hand, the oxygen cost of ventilation may be quite high, even in these subjects who do not reach limitation, ie 10-15% of the total body  $\dot{V}O_2$  cost which would represent a substantial potential "steal" of blood flow and oxygen consumption from locomotor muscles.

The greater the level of physical fitness, the greater the maximum exercise load achieved, the greater the probability that mechanical limitation to flow on expiration and to pressure generation by inspiratory muscles on inspiration will be achieved over a substantial part of the tidal breath. This results in an even higher oxygen cost of respiration in those subjects that reach mechanical limitation. On the other hand, it is only in very rare instances that we observed that this mechanical limitation interfered with the provision of sufficient alveolar hyperventilation to achieve adequate gas exchange and arterial oxygenation and acid-base regulation.

We have shown that the healthy human diaphragm will show significant fatigue as a result of its usage during endurance type exercise. The fatigue lasts more than one hour following the exercise before complete recovery is achieved. The fatigue occurs in both the fit and the unfit; however, the more fatigue occurs the more the diaphragm is used during the

exercise and the greater the work intensity achieved during the exercise.

Hypoxia brings the pulmonary system into greater and greater prominence as a limiting factor to exercise, the greater the hypoxia and the fitter the subject. Thus, exercise induced arterial hypoxemia, probably induced by diffusion limitation in the lung, occurs readily at even moderate degrees of hypoxia in above average fit subjects. Because hypoxia promotes greater ventilatory demand, limitations to expiratory flow and to inspiratory muscle pressure generation are reached at lower work-rates during hypoxic exercise. Finally, in limited trials we have seen the diaphragm become fatigued during endurance exercise in hypoxia to about the same extent as it did in normoxia, only in one half the exercise time.

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[In addition to these published manuscripts, a total of 9 abstracts, each accompanied by a presentation at a national meeting, have been published on the completed research].